Improved Delivery of Radiolabeled Anti-B1 Monoclonal Antibody to Raji Lymphoma Xenografts by Predosing with Unlabeled Anti-B1 Monoclonal Antibody

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ABSTRACT

A human B-cell lymphoma xenograft model was used to test whether the administration of unlabeled MoAb prior to injection of radiolabeled monoclonal antibody (MoAb) improves delivery of the radiolabeled MoAb to tumor prior to testing in clinical radioimmunotherapy trials. The anti-B1/CD20 pan-B-cell MoAb reactive with human B-cell lymphomas and leukemias but not reactive with mouse B-cells was used in this study. Athymic nude mice bearing human Raji Burkitt lymphoma xenografts were given injections of 2.5 μCi (0.3 μg) 131I-labeled anti-B1 with or without a 2-h prior single injection of 100 μg of unlabeled anti-B1 antibody. Four days later the animals gained injections of 131I-labeled anti-B1 and the unlabeled anti-B1 predose had a tumor uptake of 12.72 ± 1.17% (SEM) of injected dose/g which was 44% greater than the animals receiving the 131I-labeled anti-B1 alone (P = 0.014). The uptake in most normal tissues was unchanged, although the blood level of 131I-labeled anti-B1 appeared to be greater following unlabeled anti-B1 predosing (P = 0.067). Predosing with isotype matched irrelevant MoAb did not result in a greater tumor uptake or blood concentration of 131I-labeled anti-B1 compared to the administration of 131I-labeled anti-B1 alone.

In studies using 111In-labeled anti-B1, the effect of unlabeled antibody predosing was more pronounced. For animals given injections of 4.5 μCi (0.4 μg) 111In-labeled anti-B1 and the unlabeled anti-B1 predose, the uptake in tumor was 12.37 ± 2.07% of injected dose/g which was 162% greater than the animals receiving the 111In-labeled anti-B1 alone (P = 0.009). Predosing decreased 111In-labeled anti-B1 uptake in spleen, while the blood level was significantly greater.

Predosing was more effective than simultaneous injection in improving tumor delivery. When tumor-bearing mice were either simultaneously given injections of 36 μg of unlabeled anti-B1 and 4 μg 111In-labeled anti-B1 or were given preinjections of 36 μg unlabeled anti-B1 3 h prior to injection of 4 μg 111In-labeled anti-B1, tumor uptake 3 days later was 1.3-fold higher in the animals which received the preinjection of unlabeled antibody (P = 0.011). As the quantity of unlabeled anti-B1 was increased (36, 96, 996 μg) in the predose, significantly greater uptake in tumor was observed, although this uptake appeared to plateau at the highest preinjections.

It thus appears that unlabeled pan-B-cell MoAb predosing results in superior targeting of subsequently administered radiolabeled anti-B1 MoAb to tumor. Since it is unlikely that free antigen or tumor cells are present in the circulation in this animal model, it appears that blocking of specific anti-B1 Fc receptor sites by unlabeled anti-B1 predosing is involved in the enhanced tumor uptake. These results may have significant impact on the way in which radiolabeled pan-B-cell MoAbs should be delivered in clinical trials.

Received 6/6/91; accepted 11/11/91.

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This investigation was supported by National Cancer Institute Grants P01 CA47678 and RO1 CA43368.

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INTRODUCTION

One new approach to the treatment of malignancies involves the use of radiolabeled MoAbs that recognize tumor-associated antigens. This approach is particularly attractive in the case of non-Hodgkin’s lymphoma because the tumor cells of these lymphomas display a variety of tumor-associated antigens on their cell surfaces which are available for targeting (1), and because lymphoma cells are generally highly sensitive to radiation (2). A number of murine MoAbs have been developed which recognize antigens on both malignant and normal human B-cells (1, 3, 4). Since more than 75% of all non-Hodgkin’s lymphomas are of B-cell lineage, several groups of investigators, including our own (5–12), have begun to investigate the diagnostic and therapeutic use of radiolabeled pan-B-cell MoAbs in preclinical and clinical studies. We have been able to demonstrate, by using a nude mouse model of xenografted human B-cell lymphomas, that radiolabeled pan-B-cell antibodies can be specifically targeted to human B-cell tumors in vivo (11, 12), and that these radiolabeled antibodies can have therapeutic effects (13, 14).

Successful imaging in B-cell lymphoma patients has been observed (5–10) by using 131I-labeled pan-B-cell antibodies, although the degree to which all known tumor sites can be visualized appears to vary. Nonetheless, these studies demonstrate that radiolabeled antibody localization can be achieved despite the presence of target antigen on normal as well as on malignant cells. Encouraging preliminary clinical therapy data, using these reagents in patients with refractory B-cell lymphoma or leukemia have also been obtained (5–10), but much remains to be learned concerning the optimum means of delivery of these reagents.

Among the factors that could limit lymphoma targeting of radiolabeled pan-B-cell MoAbs are the following: a) complexation of administered antibody with free circulating target antigen; b) cross-reactivity with antigen-positive circulating lymphoma cells, normal B-cells in the blood or spleen, or normal non-lymphoid tissues; and c) nonantigenic binding of antibody, such as Fc binding. Evidence for each of these has been shown in animal models. All of these factors operate in human lymphoid tumor systems.

In this report we have administered unlabeled MoAb prior to injection of radiolabeled MoAb (predosing) which we hypothesize should block radiolabeled antibody binding to accessible cross-reactive nontumor sites and improve tumor delivery. In these studies we used radiolabeled anti-B1 pan-B-cell antibody (anti-CD20) to Raji Burkitt lymphoma xenografts in athymic nude mice with and without predosing with unlabeled anti-B1 antibody. We also chose to evaluate both 131I and 111In radionuclides in view of the known differences in their biodis-
tribution patterns when conjugated to MoAbs. In this animal model, there is no evidence of circulating B-cell antigen or cross-reactivity of the anti-B1 antibody with normal mouse B-cells. It was found that unlabeled anti-B1 predosing led to improved tumor delivery of radiolabeled anti-B1 antibody, likely through blocking of specific anti-B1 Fc receptor sites.

**MATERIALS AND METHODS**

Monoclonal Antibodies. The murine MoAb, anti-B1, is an IgG2a that immunoprecipitates a M, 35,000 cell surface phosphoprotein (CD20) expressed by normal human B-cells in various stages of differentiation, follicular and diffuse B-cell lymphomas, and various lymphoid leukemias (15). No reactivity of this antibody has been demonstrated with human granulocytes, platelets, thymus tissue, and T-cells (15). MS is an immunoglobulin subclass-matched irrelevant MoAb nonreactive with human tissue, blood cells, and serum proteins. It was derived from clone 7T4-1F5 hybridoma cells produced from spleen cells of a normal mouse fused with NS1/Ag4 cells. The anti-B1 and MS antibodies were provided in purified form by Coulter Immunology (Hialeah, FL).

Preparation of Labeled Antibody. Anti-B1 and MS antibodies were labeled by using the Iodo-Gen method (16, 17). 125I (ICN Biomedical, Inc., Irvine, CA) was used. Chelated anti-B1 was provided with a mixture of 1-(p-isothiocyanatobenzyl)-3-methyl-diethylenetriaminepentaacetic acid and 1-(p-isothiocyanatobenzyl)-4-methyl-diethylenetriaminepentaacetic acid chelates (18) from Coulter Immunology. The chelated anti-B1 (0.1-0.4 mg) was labeled with 0.25-2.72 mCi 111In (Amersham Corp., Arlington Heights, IL, or New England Nuclear, North Billerica, MA). Free radiometal was removed by passage over a Bio-Gel P-60 gel column (Bio-Rad Laboratories, Richmond, CA). Labeling efficiency was determined as the amount of radiouclide incorporated into the recovered product as compared to the amount of radiouclide added to the reaction mixture and thin layer chromatography. Specific activity is expressed as a ratio of mcI of radiouclide attached per mg of antibody in the final product. The percentage of protein bound 125I or 111In was determined by silica gel thin layer chromatography with the use of 0.9% NaCl solution with 0.005 M EDTA as the solvent.

**RESULTS**

Establishment of Human B-Lineage Lymphoma Xenografts in Athymic Nude Mice. The procedure to establish human B-cell tumors in athymic nude mice was similar to that described previously (12). For subcutaneous inoculation, mice were placed in a plastic holder and then exposed to 2 Gy 60Co X-irradiation at weekly intervals for 3 weeks. One day following the final dose, animals were given s.c. injections in the flank of an admixture of 1 x 10^7 Raji lymphoma cells and 5 x 10^6 HT-1080 fibrosarcoma cells in 0.2 ml RPMI 1640 medium containing 10% BCS. HT-1080 cells were lethally irradiated with 60 Gy from a 60Co irradiator before injection. Our tumors began to appear within 2-3 weeks after injection and grew in a high percentage of animals. Growing tumors were measured with a vernier caliper at regular intervals. Our experience has shown that these tumors rarely, if ever, metastasize. When the tumors were approximately 0.5-1 cm in size, the animals were distributed among the groups such that the distribution of tumor sizes within groups was comparable. Animals were given injections of radiolabeled antibodies and the biodistribution was determined. Previous studies showed that tumor uptake was not affected by variations in tumor size in this size range (11).

**Biodistribution Studies.** In vivo tissue distribution was conducted in non-tumor bearing BALB/c mice and in groups of nude mice bearing s.c. human Raji Burkitt lymphoma xenografts. Blood samples were obtained (0.6 ml average by cardiac puncture), and tissues and organs were immediately removed, rinsed with saline, blotted dry, and placed in 12- x 75-mm plastic tubes and weighed. The samples of blood, tumor, spleen, liver, heart, lung, kidney, muscle, skin, small intestine, stomach, and femur were counted in a well-type gamma counter. All animals given injections of radioiodinated antibody received potassium iodide in their drinking water starting 1 day prior to administration of radiolabeled antibody to block thyroid uptake of free iodine. Results of labeled antibody biodistribution are expressed % ID/g and as T/NT uptake ratios of the concentration (cpm per g) in the tumor relative to the normal tissue. The differences in biodistribution results produced with and without unlabeled antibody predosing were analyzed by using a one-tailed two-sample t test or by analysis of variance of antibody uptake data (19). Confidence intervals were also determined. The data were log transformed before analysis to equalize the variances within classes. Significant differences were judged present if the P value was <0.05, while a tendency to significance was judged present for a P value of 0.050-0.100.

**RESULTS**

131I-Labeled Anti-B1 Biodistribution Studies. To determine whether unlabeled specific antibody predosing could result in improved tumor delivery of 131I-labeled antibody, groups of 9 female nude mice bearing s.c. Raji xenografts were given injections i.p. of 2.5 μCi (0.3 μg) 131I-labeled anti-B1 with or without a 2-h prior single i.p. injection of 100 μg of unlabeled anti-B1 antibody. The biodistribution of labeled antibody at 4 days after injection is shown in Fig. 1. The animals given injections of 131I-labeled anti-B1 and the unlabeled anti-B1 predose had a 44% greater tumor uptake than animals receiving 131I-labeled anti-B1 alone, mean ± SEM of 12.72 ± 1.17% ID/g versus 8.83 ± 1.01% ID/g (P = 0.014). The uptake in most normal tissues was unchanged by unlabeled anti-B1 predosing. However, the blood level of 131I-labeled anti-B1 appeared to be greater follow-

* Unpublished observations.
To separate further the effects of total antibody dose from the effects of the timing of administration of unlabeled antibody, groups of 6 male nude mice bearing s.c. Raji xenografts were either simultaneously injected i.v. with 36 µg unlabeled anti-B1 and 4 µg 111In-labeled anti-B1 or preloaded with 36 µg unlabeled anti-B1 i.v. 3 h prior to an i.v. injection of 4 µg 111In-labeled anti-B1. Both groups of animals were sacrificed 3 days later. The biodistribution results are shown in Fig. 3. Again, predosing resulted in superior tumor delivery. The uptake in tumor was 20.92 ± 3.22% ID/g for the mice that received a predose which was 134% higher than the animals receiving the 111In-labeled anti-B1 with unlabeled anti-B1 simultaneously (P = 0.011). The uptake in normal tissues was not significantly different between the two groups (P > 0.050). The T/NT uptake ratios were significantly greater following unlabeled anti-B1 predosing for liver, skin, bone, heart, kidney, small intestine, testes, and spleen with predosing (P < 0.050).

Fig. 4 displays the effect of predosing with different quantities of unlabeled anti-B1 injected i.v. on the distribution of 111In-labeled anti-B1 administered i.v. 3 h later. As the quantity of unlabeled anti-B1 was increased (36, 96, 996 µg) in the predose, significantly greater uptake in tumor was observed at 3 days, although this uptake appeared to plateau at the highest predoses. This was accompanied by an increase in 111In-labeled anti-B1 in blood and a decrease in uptake in the spleen. The uptake in lung, muscle, liver, bone, and brain all were

**Fig. 1. Biodistribution of 2.5 µCi (0.3 µg) 111In-labeled anti-B1 in groups of 9 female athymic nude mice bearing Raji Burkitt lymphoma xenografts and receiving (□) no unlabeled anti-B1 or (■) 100 µg unlabeled anti-B1 MoAb 2 h earlier. Sacrifice was at 4 days following i.p. injections with the % ID/g in tissues calculated. n, number of animals/group; bars, SEM. * BL, blood; HT, heart; * LU, lung; LI, liver; SI, small intestine; SP, spleen; KI, kidney; * SK, skin; BN, bone; MS, muscle; * TU, tumor. * P < 0.067.**

**Fig. 2. Biodistribution of 4.5 µCi (0.4 µg) 111In-labeled anti-B1 in groups of 7 female athymic nude mice bearing Raji Burkitt lymphoma xenografts and receiving (□) no unlabeled anti-B1 or (■) 100 µg unlabeled anti-B1 2 h earlier. At 4 days following i.p. injections animals were sacrificed and the % ID/g in tissues was calculated. n, number of animals/group; bars, SEM. * BL, blood; HT, heart; * LU, lung; LI, liver; * SI, small intestine; SP, spleen; * KI, kidney; * SK, skin; BN, bone; MS, muscle; * TU, tumor. * P > 0.049.**

**Fig. 3. Uptake (mean % ID/g ± SEM) at 3 days after i.v. injection of 4 µg 111In-labeled anti-B1 administered (□) simultaneously with 36 µg unlabeled anti-B1 or (■) 3 h after i.v. injection of 36 µg unlabeled anti-B1 in groups of 6 male nude mice bearing Raji lymphoma xenografts. The uptake in tumor was significantly different (P = 0.011), whereas the differences in most normal tissues were not significantly different (P > 0.050). BL, blood; HT, heart; LU, lung; LI, liver; SI, small intestine; SP, spleen; KI, kidney; SK, skin; BN, bone; MS, muscle; TE, testes; BR, brain.**
We have studied has not been shown to cross-react with normal clinical situation is that the anti-Bl mouse pan-B-cell MoAb were either simultaneously given injections of unlabeled anti-Bl, we do not think that this difference in route of administra...

DISCUSSION

In this study we examined the effect of unlabeled antibody predosing as a means of improving tumor delivery of radiolabeled pan-B-cell MoAb in a nude mouse human lymphoma xenograft model. Our hypothesis was that unlabeled antibody predosing in lymphoma patients would increase tumor delivery of radiolabeled antibody by competitive binding with circulating lymphoma cells, free tumor antigen, or Fc binding sites. A limitation of this model in terms of its applicability to the clinical situation is that the anti-Bl mouse pan-B-cell MoAb we have studied has not been shown to cross-react with normal mouse cells (20), whereas most of the available pan-B-cell MoAbs show cross-reactivity with normal B-cells in human peripheral blood and well-vascularized organs. However, the model has the feature that it can help to dissect out certain aspects such as the effects of circulating antigen or the role of Fc binding.

In this study we demonstrated that unlabeled anti-Bl antibody predosing could lead to greater tumor delivery of 131I- and 111In-labeled anti-Bl in a human lymphoma xenograft model compared to 131I- or 111In-labeled anti-Bl administration alone. The T/NT uptake ratios were greater for most tissues after unlabeled antibody predosing. Our results in tumor-bearing mice showed a decline in spleen uptake of 111In-labeled anti-Bl following a 100-μg anti-Bl predose compared to no predosing. The uptake in most other normal tissues was unchanged by unlabeled anti-Bl predosing, although the blood level of 131I-Bl was also studied. As the quantity of unlabeled anti-Bl was increased in the predose, significantly greater uptake in tumor was observed, although this uptake appeared to plateau at the highest predoses, suggesting that there may be an optimum level of unlabeled antibody to administer with the possibility that higher predoses might decrease tumor uptake due to saturation of tumor with unlabeled antibody. We have yet to determine the optimal predose level. Tumor saturation has been described in other systems (22), hence it will be important to investigate the high dose interval in patient trials.

In our studies, we chose to use counting of tissues rather than imaging to evaluate changes in localization, because this is a more sensitive assay involving counting of the tissue alone and eliminates the contribution of overlying tissue activity to the image. In relation to therapy, no conclusions can be drawn until dosimetry estimates of absorbed doses are obtained in this animal model system, which is beyond the scope of this paper.

In this model, predosing with an irrelevant isotype-matched control antibody did not increase the uptake of 131I-labeled anti-Bl antibody in tumor or blood. This supports the concept that the greater tumor delivery of radiolabeled anti-Bl pan-B-cell MoAb with predosing was likely due to the increased availability of radiolabeled anti-Bl MoAb following unlabeled antibody predosing, due to competitive binding of the unlabeled antibody to a specific receptor. Candidate specific receptors include circulating antigen, circulating tumor cells, or specific Fc receptor binding sites in various normal tissues. The CD20 antigen recognized by anti-Bl is not shed from the tumor cell surface and does not modulate in response to MoAb binding (23). Indeed, we found no evidence for the release of B1 antigen in vitro when supernatants from cultured Raji cells were incubated with varying dilutions of unlabeled anti-B1 and Raji cells in an indirect immunofluorescence inhibition assay (data not shown). This suggests that it is unlikely that there would be circulating antigen in this animal model. At the present time there is no conclusive evidence of circulating tumor cells in this animal model. By fluorescent microscopy we have not been able to detect a significant number of B1-positive cells in mouse blood. In addition, we did not observe any metastatic lesions in the mice, which argues against a significant number of circulating tumor cells. This makes a specific receptor for anti-Bl a more prime candidate in this animal model. Evidence for specificity of Fc receptor binding by MoAbs has recently been demonstrated by genetic manipulation of amino acids in the C1 domain of human IgG (24). It is possible that there is a specific receptor that binds anti-B1, that does not bind the isotype-matched control immunoglobulin.

Varying results have been reported with regard to predosing. Some investigators have demonstrated in patients with colon cancer the formation of anti-CEA antibody complexes with circulating CEA, but despite this, antibody localization could still be detected in tumor (25, 26). However, experiments with athymic nude mice bearing CEA-producing colon cancer xenografts demonstrated that large amounts of CEA in serum resulted in higher uptake of 111In-labeled anti-CEA MoAb in the liver and lower uptake in tumor, whereas with 125I-labeled
anti-CEA MoAb there was lower uptake in both tumor and liver (27–29). Beatty et al. (27, 28) showed that administration of a predose of unlabeled anti-CEA MoAb to athymic nude mice bearing LS174T human colon cancer xenografts produced CEA-MoAb complexes which significantly decreased normal liver uptake and increased tumor uptake of 111In-labeled anti-CEA MoAb, whereas pretreatment with nonspecific MoAb was ineffective in decreasing liver uptake or increasing tumor uptake. A loss of the predosing effect was observed when unlabeled specific antibody was administered simultaneously with radiolabeled antibody. Murray et al. (30) showed in humans that liver, spleen, and bone uptake of 111In-labeled 96.5 anti-melanoma antibody with respect to heart (blood pool) uptake could be decreased by predosing with unlabeled specific antibody, compared to an identical dose of unlabeled nonimmunoreactive MoAb. It was hypothesized that saturation of receptor sites in the liver by unlabeled specific antibody might be due to cross-reactivity with the P97-specific antigen, reactive with the 96.5 MoAb, in the liver. In contrast, we have previously shown that in athymic nude mice with melanoma xenografts, a system known not to have detectable circulating antigen, that tumor uptake and T/NT uptake ratios were not substantially enhanced by the prior administration of unlabeled antibody (31). In a limited series of 4 patients with B-cell lymphoma, DeNardo et al. (32) reported in an abstract that a predose of 4–5 mg unlabeled Lym-1 (another pan-B-cell antibody) led to a slower blood clearance of radioactivity than when 125I-labeled Lym-1 alone was administered to the same patients. It was hypothesized that the mechanism involved saturable hepatic Fc receptors based on prior animal data. In contrast, Eary et al. (33) reported that the serum half-life of 99mTc-labeled 9.2.27 Fab'2 fragments was increased in patients with melanoma following the injection of unlabeled intact irrelevant antibody compared to no predosing, and the percentage of known tumor sites imaged increased in patients predosed with irrelevant antibody.

Despite target antigen expression on normal B-cells, 131I-labeled pan-B-cell MoAbs have been used successfully to image and treat patients with B-cell lymphomas (5–10). The dose of unlabeled antibody administered at the same time as radiolabeled antibody in a clinical study has been found to influence delivery of the radiolabeled antibody to tumor in patients. Press et al. (7) reported that tumor localization and retention of 131I-labeled MB-1 was greater when labeled antibody was infused simultaneously with a high dose of unlabeled antibody (10 mg/kg) than with low (0.5 mg/kg) or intermediate (2.5 mg/kg) doses. It is intriguing to speculate, based on our results, whether predosing would have further improved resulting biodistributions. We are currently testing the effect of various levels of unlabeled antibody predose in a clinical trial of 131I-labeled anti-B1 in patients with B-cell lymphoma (34), and preliminary data indicate that the predosing effect can enhance tumor targeting in some patients.

As far as we are aware, the present study is the first to show that predosing with an unlabeled pan-B-cell MoAb leads to increased delivery of radiolabeled antibody to human B-cell lymphoma xenografts. Evidence of similar findings were obtained in a different tumor model of mouse T-cell lymphoma and anti-Thy-1.1 MoAb (35). It was found that predosing of AKR/J (Thy-1.1+) mice bearing s.c. SL2 Thy-1.1+ T-cell lymphoma with unlabeled MoAb against the Thy-1.1 antigen led to a progressive increase of 131I-labeled anti-Thy-1.1 in tumor. The concentration of radiolabeled antibody in blood was slightly higher in mice that were pretreated. The increase in tumor concentration following unlabeled antibody predosing was thought to be due to blocking of 131I-labeled anti-Thy-1.1 antibody binding to normal T-lymphocytes or elimination of these cells with resulting prolongation of serum clearance of the labeled antibody. Sharkey et al. (36) reported that the uptake of 131I-labeled EPB-2 IgG2a MoAb, reactive with human B-cell lymphoma, in Raji xenografts paralleled blood levels, being low in mice with rapid blood clearance. These investigators also reported that the simultaneous injection of unlabeled IgG2a MoAbs inhibited the rapid blood clearance of radioiodinated MoAbs in outbred nude mice. It should be noted that the mice used in our studies were of BALB/c background and displayed a normal blood clearance rate as defined by Sharkey et al. (36). Adams et al. (37) reported that a 0.2-µg dose of 111In-labeled Lym-1 antibody resulted in higher liver and spleen uptake (% ID/g) in normal BALB/c mice than after a 20-µg dose. It was hypothesized that the higher dose injected saturated available receptors. In contrast, we found no differences in liver, spleen, or kidney uptake following injection of 1, 4, or 16 µg of 111In-labeled anti-B1 in normal mice.

In our studies we found the effect of predosing to be more pronounced when the antibody used was labeled with 111In rather than with 131I. The basis for this finding is not completely understood. It is known that 111In- and radioiodine-labeled MoAbs show different biodistributions due to dehalogenation of radioiodine-labeled MoAbs and retention of 111In-labeled MoAbs within cells. Naruki et al. (38) for instance found that human lymphoma and leukemia cells showed higher retention of 111In-labeled T101 anti-CD5 MoAb than of 125I-labeled T101 antibody, suggesting differences in intracellular catabolism and retention of the radionuclides. The applicability of these studies to our findings is complicated, however, by the fact that the T101/CD5 complex undergoes significant modulation and internalization (39, 40) which may be key to these results. In contrast, the anti-B1/CD20 complex is not known to undergo significant modulation and internalization (23, 41).

In summary, our data indicate that in this murine model of human B-cell lymphoma, that unlabeled antibody predosing with unlabeled specific antibody can substantially enhance tumor binding by radiolabeled anti-B1 antibody and decrease antibody uptake in normal tissues. The mechanism appears to involve a saturable competing specific receptor. Unlabeled antibody predosing should be explored clinically as a possible method to enhance the imaging and treatment of non-Hodgkin's lymphoma with radiolabeled pan-B-cell-reactive antibodies.

ACKNOWLEDGMENTS

The authors gratefully acknowledge Dr. Renato Del Rosario and Jeannette Roesnner for the radiolabeling of the MoAbs, Dianne Guilbault, Christina Liu, and Jeannette Roesnner for performing the binding assays, and Arthur Glafelter and Ann Petrowski for carrying out the animal biodistribution studies at the University of Michigan. We thank Paulette Smariga and Edward O'Connell of Coulter Immunology Division for the radiolabeling, binding assays, and animal biodistribution studies. We thank Renee Kite for typing the manuscript.

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